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| 09/649,108 | 08/28/2000 | Lieping Chen | 07039-220001 | 7772 |

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| EXAMINER | |
|---|---|
| ROARK, JESSICA H | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | 15 |

DATE MAILED: 05/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/649,108 | Applicant(s) CHEN, LIEPING | |
|---|---|---|---|
| | Examiner Jessica H. Roark | Art Unit 1644 | |

*-- The MAILING DATE of this communicati n appears on the cover sheet with the c rrespondence address --*

**Period f r Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *1-5,8 and 10-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. *Claims* 1-48 *are pending.*

2. Applicant's election without traverse of Group II (claims 6-10) and a species of SEQ ID NO:1 in Paper No. 14 is acknowledged.

Claims 1-5, 8 and 10-48 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention or species.

*Claims* 6-7 and 9 *are under consideration in the instant application.*

3. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

**A. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

**B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.**

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

**Timing of Corrections**

*Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in* ***ABANDONMENT*** *of the application.*

5. Applicant should avoid the use of "novel" in the title and abstract, as patents are presumed to be novel and unobvious.

6. USSN 09/451,291 appears to provide adequate written support for the instant claims.

7. Applicant's IDSs, filed 8/16/01 and 11/15/00 (Paper Nos. 7 and 12), are acknowledged.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. The disclosure is objected to because it contains an embedded hyperlink at least on page 15 at line 29. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01. In addition, Applicant is requested to review the application for additional hyperlinks and/or other forms of browser-executable code and delete them. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. See MPEP § 608.01 and 608.01(p).

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

11. Claims 6-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide of SEQ ID NO:1; does not reasonably provide enablement for any "polypeptide with *the ability to costimulate a T cell*" encoded by a nucleic acid "*that hybridizes* under stringent hybridization conditions to the complement of a sequence that encodes SEQ ID NO:1"; a "*fragment*" of the polypeptide of SEQ ID NO:1; or an amino acid sequence differing from residues 23 to 290 of SEQ ID NO:1 (or fragments thereof) solely by *"conservative substitutions"*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The instant claims encompass in their breadth *any* polypeptide that shares some minimal degree of structural relatedness to the polypeptide of SEQ ID NO:1 by virtue of being encoded by a nucleic acid which "hybridizes under stringent conditions" to the complement of a sequence that encodes SEQ ID NO:1, by differing solely by conservative substitutions, or that is a fragmentary sequence of any of these "related" polypeptides; so long as the related polypeptide or fragment thereof possesses *any* function that may be broadly considered "the ability to co-stimulate a T cell". Thus the breadth of the instant claims is extensive, encompassing numerous structural and functional variants of the polypeptide of SEQ ID NO:1.

Applicant has disclosed a nucleic acid sequence (SEQ ID NO:2) encoding a polypeptide (SEQ ID NO:1) with disclosed "co-stimulatory" activities including enhancing T cell proliferation and preferential IL-10 secretion from activated T cells (e.g., page 35). Applicant has also disclosed a mouse polypeptide (SEQ ID NO:3 encoded by SEQ ID NO:4) with these activities (e.g., pages 37-39).

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the numerous variants and fragments of SEQ ID NO:1 encompassed by the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for the limited testable functions of enhancing T cell proliferation and preferential IL-10 secretion from activated T cells. Even greater guidance would be required for the skilled artisan to select essential sequences and sequence lengths for the more ambiguous function of "the ability to co-stimulate a T cell" since, as noted below, not only are many functions encompassed by this phrase, but the functions may be mutually exclusive with respect to any particular structure.

Further, the fact that two nucleic acid sequences will hybridize under some undefined "stringent conditions" does not in and of itself require that polypeptides encoded by the two sequences/sequence complements share any functional activity. It was well know in the art at the time the invention was made that hybridization could occur between *fragments* of two sequences, and so does not require that the full length of a referenced SEQ ID NO: be shared. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible, leading to extensive variation in the encoded polypeptide. Finally, hybridization under conditions other than high stringency would be expected to permit a great deal of variation between the two hybridizing sequences, making it even more unpredictable that polypeptides encoded by the hybridizing sequences/sequence complements would share any function.

Thus hybridization language in the absence of *a testable function* and limitations regarding both the *hybridization conditions* and the *sequence length over which the hybridization takes place*; does not allow the skilled artisan to make and use polypeptides encoded by hybridizing nucleic acids commensurate in scope with the instant claims without undue experimentation. Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the skilled artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). This requirement is emphasized in the instant example since, as summarized in Figures 2 and 3 of Coyle et al. (Nature Immunol. 2:203-209 2001) the B7-like family members have distinct expression patterns and distinct functions, *even though they share some degree of similar overall structure.*

The claims also recite sequences which "differ solely by conservative substitutions". However the skilled artisan was well aware that even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 (B7-1) and CD86 (B7-2 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides differing even in only conservative substitutions.

In addition, the instant claims encompass fragments of the aforementioned polypeptides due to the absence of a requirement that hybridization be over the full length; and in view of the use of "a" and "an", indefinite articles which when used in contexts such as "an amino acid sequence of ..." indicates that subsequences of the referenced SEQ ID NO: are also encompassed by the claim language. Although Applicant has provided a working example of a fragment comprising the extracellular domain which can enhance T cell proliferation and IL-10 production (e.g., pages 34-35 and Figures 2a and 12a), the skilled artisan would not be able to reasonably predict without undue experimentation which other fragments of SEQ ID NO:1 would share these activities (even if they were required functional limitations). In addition, it would be even more unpredictable as to which fragments of the "variants" of SEQ ID NO:1 encompassed by the hybridization and substitution language would share these activities.

Thus although the level of skill in the art is high, without detailed direction as to which sequences and sequence lengths are essential to the function of the encoded polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of sequences encompassed by the instant claims would share the disclosed functions of the polypeptide of SEQ ID NO:1. Without sufficient guidance as to a distinct and testable function possessed by the recited polypeptides; the changes which can be made in these polypeptides and still maintain the broad function of "the ability to co-stimulate a T cell" are unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. Claims 6-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following written description rejection is set forth herein.

Applicant has disclosed a nucleic acid sequence (SEQ ID NO:2) encoding a polypeptide (SEQ ID NO:1) with disclosed "co-stimulatory" activities including enhancing T cell proliferation and preferential IL-10 secretion from activated T cells (e.g., page 35). Applicant has also disclosed a mouse polypeptide (SEQ ID NO:3 encoded by SEQ ID NO:4) with these activities (e.g., pages 37-39).

The instant claims are drawn to a genus of polypeptides which share some minimal degree of structural relatedness to the polypeptide of SEQ ID NO:1 by virtue of being encoded by a nucleic acid which "hybridizes under stringent conditions" to the complement of a sequence that encodes SEQ ID NO:1, by differing solely by conservative substitutions, or that is a fragmentary sequence of any of these "related" polypeptides. In addition, the recited polypeptides possess *any* function that may be broadly considered "the ability to co-stimulate a T cell". As noted below, although the phrase "the ability to co-stimulate a T cell" does indicate some functionality shared by the polypeptides; numerous and mutually exclusive functions are encompassed by this phrase. Therefore, "the ability to co-stimulate a T cell" does not provide a meaningful function that can be correlated with any particular structural aspect shared by the variant polypeptides and fragments recited in the instant claims.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Consequently, the claimed invention is not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the invention. See Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

14 Claims 6-7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 6 and dependent claims 7 and 9 are indefinite in that claim 6 is dependent on a non-elected claim. Claim 6 should be written as an independent claim.

B) Claim 6 is ambiguous in the recitation in claim 1, from which claim 6 depends, of "a polypeptide with an amino acid sequence *with* SEQ ID NO:1". It is unclear what the relationship of the first polypeptide is with respect to the reference SEQ ID NO:.

It is suggested that Applicant amend the claim to recite language such as -- a polypeptide with *an* amino acid sequence *of* SEQ ID NO:1 -- , or -- a polypeptide with *the* amino acid sequence *set forth in* SEQ ID NO:1 -- depending upon whether the claim is intended to encompass fragments of SEQ ID NO:1 or not.

C) Claims 6-7 and 9 are indefinite in the recitation via their dependency on non-elected claim 1 of "stringent conditions", as it is unclear to what conditions the claims are drawn. Stringency of hybridization condition can be considered either "low", "moderate", or "high"; encompasses both salt concentrations and temperature of hybridization; and determines the degree of complementarity needed for one nucleic acid molecule to hybridize to another. Absent a clear definition as to these parameters, the claims are indefinite as it cannot be determined what type of hybridization conditions are encompassed by the instant claims, in turn prohibiting a determination of the degree of complementarity possessed by the nucleic acid sequence which hybridizes to the complement of SEQ ID NO:1.

It is noted that the specification discloses specific parameters on page 16 at lines 1-8 which could be recited to avoid the ambiguity associated with the instant claim language.

D) Claims 6-7 and 9 are ambiguous in their recitation (via their dependency on non-elected claim 1) of a polypeptide with the "ability to co-stimulate a T cell". The specification discloses on page 6 at lines 21-29 that mutually exclusive functions are encompasses by the term "co-stimulates", because although the term is used to indicate that a function is "enhanced" (e.g. line 22), the functions may be either activating (i.e., effector and helper responses) or suppressive.

It is suggested that Applicant amend the claims to recite *a defined and testable function*, supported in the specification as-filed, such a enhancing proliferation of T cells or enhancing production of IL-10 by activated T cells (e.g., pages 13, 35-36 and 37-39).

E) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.*

*The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).*

16. Claim 6 is rejected under 35 U.S.C. 102(e) as being anticipated by Ostrand-Rosenberg et al. (U.S. Pat. No. 5,858,776, see entire document).

Ostrand-Rosenberg et al. teach that SEQ ID NO:1 of '776 encoding SEQ ID NO:2 of '776 is a human B7 polypeptide that co-stimulates T cells when transfected into tumor cells (see entire document, especially columns 7 and 21-22). SEQ ID NO:1 of Ostrand-Rosenberg et al. encodes a polypeptide having 26.6% similarity to instant SEQ ID NO:1. In view of the indefinite claim language with respect to "hybridizes under stringent conditions", as noted supra, Ostrand-Rosenberg et al.'s SEQ ID NO:2 encoded by SEQ ID NO:1 meets the limitation of an isolated polypeptide that co-stimulates a T cell and that is encoded by a DNA that "hybridizes under stringent conditions" to the complement of a sequence that encodes an amino acid sequence with SEQ ID NO:1. It is further noted that the instant claim language reads on fragmentary sequences of instant SEQ ID NO:1 since the hybridization is not required over the full length and in view of the language "*a* polypeptide with *an* amino acid sequence".

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitation of co-stimulating T cells is an inherent property of the polypeptide of SEQ ID NO:2 encoded by SEQ ID NO:1 of Ostrand-Rosenberg et al.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
May 14, 2002

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
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5/14/02